PROPHYLACTIC THEOPHYLLINE INFUSION FOR PREVENTION OF APNEA OF PREMATURITY

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ABSTRACT

To assess if there was any advantage in the prophylactic use of theophylline to prevent apnea in preterms, we treated 56 preterms (Group A) <34 weeks gestation with theophylline infusion and compared these with 25 age and weight matched preterms (Group B) who received no therapy. Aminophylline (25 mg/ml) was infused from admission in all neonates (group A) at rates ranging 0.2 to 0.38 mg/kg/h and blood levels estimated on an Abbots TDX analyser by Fluorescence Polarization Immunoassay, after 5 days infusion. All neonates (Groups A+B) were monitored on a Corometric 505 neonatal monitor.

In Group A, 1/48 developed primary apnea while in Group B, 4-21 had primary apnea ($p<0.05$). Serum theophylline ranged from 2.3 to 39.5 μg/ml with a mean of 12.7 μg/ml. The mean serum level of theophylline in 4 cases who exhibited clinical evidences of toxicity was 30.1 μg/ml. A statistically significant difference ($p<0.05$) was noted in birth weight and serum level inspite of similar infusion rates of theophylline. A linear correlation $r = 0.65$ was noted between serum level and infusion rate. Multivariate regression analysis, between birth weight and gestational age to serum level, showed a linear correlationship only between birth weight and serum level ($r = 0.45$).

Key words: *Apnea, Prematurity, Theophylline, Prophylaxis*

In most nurseries in our settings, electronic apnea monitors and pulse oximetry are not available. Hence by the time an apneic episode is visually observed, the ill effects of hypoxia have often already set in. To assess if there was any advantage in the prophylactic use of theophylline for prevention of apnea of prematurity, we conducted a prospective, non randomized, non blinded, controlled trial in preterms admitted to our nursery. We also aimed to define the optimal dose and blood level and identify factors affecting serum concentration and side effects of theophylline.

Material and Methods

Fifty six preterms between 28 and 34 weeks gestation and 800 to 2000 g birth weight without clinical evidence of respiratory distress or sepsis who were less than 24 hours of age formed the study Group A. Injection aminophylline (25 mg/ml) was administered from admission as a continuous infusion at rates ranging from 0.2 to 0.38 mg/kg/h in all cases. Twenty five age and weight matched preterms not given aminophylline therapy formed the control Group B. All neonates were monitored on a Corometrics Instruments Systems 505 neonatal monitor preset to detect respiratory pauses >15 seconds. Any alarm was immediately checked to ensure its authenticity and rule out false alarms due to system defects. Apnea was defined as respira-

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tory pauses >15 seconds with or without bradycardia and cyanosis(1). One ml venous blood was collected from a site other than the infusion site and estimated for theophylline level on an Abbots TDX analyser by Fluorescence Polarization Immunoassay (FPIA)(2) after five days infusion. The accuracy and the precision of the system was tested with low, medium and high controls each time a sample was run. Drug levels were available within six hours of blood collection. Theophylline therapy was continued till as long as intravenous fluids were infused.

Any neonate who developed apnea was investigated to rule out a secondary cause and where one was detected it was treated accordingly. A septic screen and lumbar puncture was done in all cases of secondary apnea suspected of having sepsis on intracranial bleed. Appropriate antibiotics were started when indicated. In those who developed apnea, Group A or B, Doxapram infusion at rates of 1-1.5 mg/kg/h was started(3,4). No attempt, however, was made in this study to compare efficacy of doxapram versus theophylline in management of apnea, as serum doxapram levels were not available and comparable numbers were few. If a neonate exhibited evidences of theophylline toxicity(5,6), a blood level was immediately estimated and the infusion stopped if serum levels were >20 μg/ml. Data was statistically analysed using the Chi Square test.

Results

In Group A (n = 56), 9 developed apnea while on therapy, 8 of whom died of a secondary cause, 6 of sepsis, 1 of meningitis and 1 of intraventricular hemorrhage(IVH). The one case where no cause for apnea was detected (true treatment failure) had a subtherapeutic serum theophylline level of 4.8 μg/ml (N = 6-12 μg/ml)(6,7) inspite of receiving 0.33 mg/kg/h of aminophyline. In Group B (n = 25), 8 developed apnea, 4 of whom had a secondary etiology. Of these, 3 died of sepsis and 1 of IVH. The mean and range of serum theophylline levels at different birth weight and gestational age is depicted in *Figs. 1 & 2.*

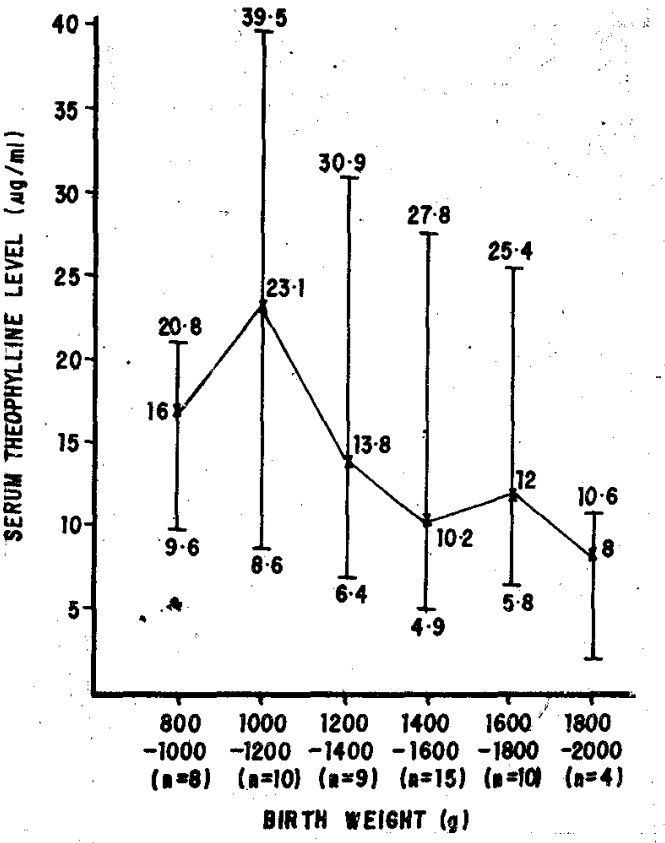

Fig. 1. Mean and range of serum theophylline level in Group A at different birth weights.

Excluding patients with secondary apnea, 1/48 in Group A and 4/21 in Group B had primary apnea ($p<0.05$). Toxic blood levels of theophylline (>20 μg/ml)(8) were observed in 8 preterms (mean level 26.6 μg/ml) of which 4 exhibited clinical evidence of theophylline toxicity (mean level 30.1 μg/ml). Tachycardia (>180/min) was observed in 2 seizures in 1 and abdominal distention with brownish gastric aspirate in one. The mean level in the remaining 48 cases in Group A was

13.2 μg/ml. A significant difference in serum level was noted between the 8 cases with toxic levels and the remaining 48 cases ($p<0.05$). A linear correlation was observed between aminophylline dose infused and serum level (*Fig. 3*) with a coefficient of correlation (r) of 0.65. Multivariate regression analysis between birth weight and gestation age to serum level showed a linear relationship only between birth weight and serum level ($r = 0.45$). A statistically significant difference ($p<0.05$) was noted in birth weight and serum level between those who had toxic versus non-toxic levels inspite of similar infusion rates of aminophylline (*Table*).

Discussion

Apneic attacks in preterms come on unheralded and pose a major problem as they carry a high risk of morbidity and mortality(9). By the time apnea is clinically detected most preterms may have already suffered hypoxic brain injury. Presently, the emphasis seems to be on monitoring hypoxia, which is the end result of an apneic episode. This may be possible by pulse oximetry which indicates the problematic apnea and alerts us to the need to intervene. Respirogenic drug therapy has a definite role in the management of apnea(7,10), however all data to date has emphasized on the rescue treatment of apnea once it has already set in. Given the problems in our setting, we embarked on this trial to assess the efficacy of prophylactic theophylline therapy for prevention of "primary" apnea of prematurity. Theophylline, a methylxanthine, crosses the blood brain barrier and stimulates the respiratory centres, it also increases diaphragmatic contractility. The role of other methods of management of apnea apart from supportive therapy, which include cutaneous stimulation,

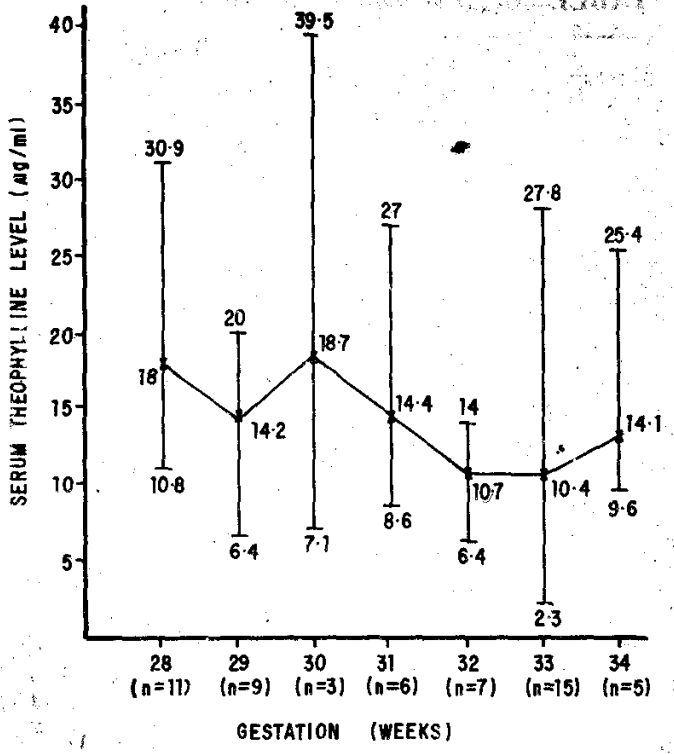

Fig. 2. Mean and range of serum theophylline level in Group A at different gestational ages.

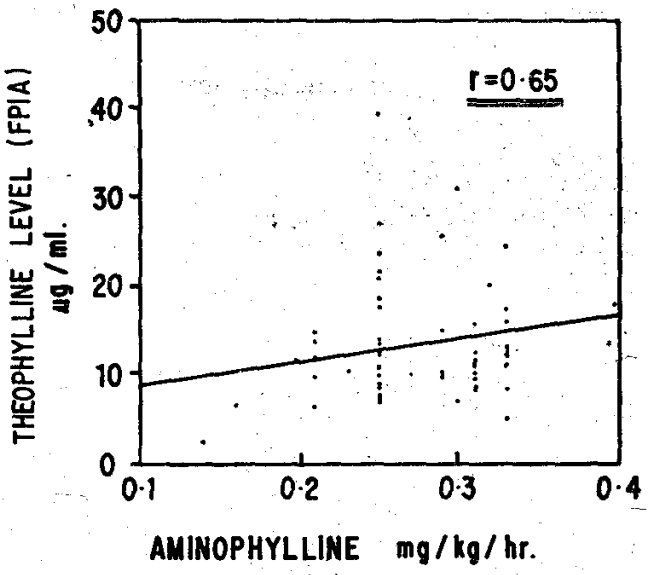

Fig. 3. Relation of serum theophylline level to its rate of infusion.

TABLE—*Mean Weight, Gestational Age and Infusion Rate Compared with Serum Theophylline Levels*

Group	No	Mean weight (g)	Mean gestation (wks)	Infusion rate (mg/kg/h)	Serum level (FPIA) (μg/ml)
Group A					
All patients	56	1300	31	0.26	13.3
Treatment failures	9	1245	30.5	0.29	12.7
Toxic levels	8	1077°	29.1	0.27	26.6*
Cenical toxicity	4	1250	30	0.29	30.1*
Non toxic levels	48	1400°	31.5	0.26	13.2*
Group B					
Controls	25	1400	31.5	— p>0.05	—

*p<0.05, °p<0.05

continuous positive airway pressure and mec hanical ventilation are not to be undermined.

Our results suggest that there is a significant difference in the incidence of primary apnea between the treated and untreated group (p<0.05) thereby suggesting that theophylline prophylaxis is effective in preventing primary apnea. Aminophylline which contains 85% theophylline(11,12) was infused at rates of 0.2 to 0.38 mg/kg/h and resulted in therapeutic levels in 46 of 56 neonates. Two had subtherapeutic and eight had toxic levels. In Group A, all 8 neonates who had secondary apnea developed apnea inspite of maintaining therapeutic drug levels, thereby suggesting that theophylline was not effective in prevention of apnea when a secondary etiology existed. The rate of theophylline infusion in those eight with toxic serum levels did not differ significantly (0.27 mg/kg/h) as compared to the remaining 48 in Group A (0.26 mg/kg/h). However, in those who had toxic levels the birth weight and gestational age was significantly lower, suggesting that the metabolism of theophylline is altered in very low birth weight and extreme preterms. The hepatic microenzymal immaturity is responsible for a prolonged halflife of theophylline (>24 hours) in very low birth weight neonates leading to its toxicity (8,13). We hence, suggest lower infusion rates and frequent monitoring of serum levels (if possible) in extreme low birth weight pretems. In settings where serum levels cannot be monitored, we do not recommend bolusing of the drug. We recommend that the dose of aminophylline ranging from 0.2 to 0.3 mg/kg/h equivalent to 0.17 to 0.25 mg/kg/h of theophylline is relatively safe if infused slowly and at the earliest evidence of toxicity, particularly seizures, the drug be withdrawn.

We conclude that the judicious routine infusion of theophylline for prevention of apnea in "at risk" preterms may be warranted, wherein apnea monitoring and hence its early detection is not possible, practicable or available given the cost and shortcomings of electronic apnea monitoring equipments(14,15).

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